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DNA

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The Double Helix

Perspective and Prospective at Forty Years

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Greetings

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I'm pleased that Donald Chambers has evoked Francis Ryan's memory: he was so important in the lives of all of his students, and I am proud to have been one of them.

I was going to start by arguing with Gunther Stent as to whether the Renaissance started at the fall of Constantinople in the fifteenth century or the recapture of Toledo and its library in the twelfth . . . but I'll spare you that. For one thing I wasn't there, so I can't speak at first hand for either of these events.

Gunther's remarks about "premature discovery" and its reception do have a lot of bearing on how we do science, so I would like to say something about that. He was right about Mendel, of course. As to the reception of "AMM44,"[1] to the contrary, I *was* there, and have a more complicated view. I just do not believe that those can be compared. This meeting offers too nearly unique a setting and audience to let that go by without comment.

Does *premature* mean:

- "the data do not exist to explain all of the paradoxes and challenges of a new discovery"?
- "the audience is incapable of understanding the challenge"?

Many of Gunther Stent's readers have interpreted premature to mean the latter; else almost every provocative discovery is in some respects premature.

I suggest that the touchstone is the reaction, not just verbally, but in the laboratory. You might see controversy and active inquiry, diligent effort to accumulate experimental data that will resolve the question, which is just what did happen from 1944 on. (The reaction to McClintock's "jumping genes" in maize, also decried as premature, was in fact similar.) Or the claim might be relegated to oblivion. Mendel's case was close to that, happily a rare event in the history of science. To pursue the receptor metaphor: the ligand can be irrelevant, or it can be an agonist, an antagonist, or even both.

My inclinations go closer to Rollin Hotchkiss's remarks that give credit to the importance of organized critical skepticism[2] in maintaining the integrity of science. Even when hindsight tells otherwise, we should be skeptical of in-

stant genuflection to new revelations. For novel claims to be challenged is a necessary and healthy aspect of scientific progress.

I had a lot of sympathy for Rollin Hotchkiss when he talked, both 40 years ago and today, about that last 1% or 0.1% of margin for protein contamination of DNA. That was fighting Avogrado's number: a formidable opponent for the exclusion of protein. As late as 1953, and after his celebrated experiment with Martha Chase, even Al Hershey had some reservations: "My own guess is that DNA will not prove to be a unique determiner of genetic specificity, but that contributions to the question will be made in the near future only by persons willing to entertain the contrary view."[3] Well, his statement was half-right! Too easily forgotten today was Wendell Stanley's error in 1935, claiming that crystalline TMV was a pure protein, only to be corrected by Pirie's finding of a few percent of RNA: a mistake no one wanted to repeat in a hurry. So we should welcome debate and the search for critical and corroborative evidence and applaud Mac McCarty for that extra, arduous repetition to seal the argument. To be ignored is only slightly worse than to be swallowed whole. And there is a lot of revision ahead even for our well established dogmas.[4]

Let me now turn to my proper role, to be the stagehand pulling up the curtain for our star event. To *introduce Jim Watson* is the oxymoron of all time. I have never seen him in a modest mood–you can puzzle whether that refers to his mood, or Francis's, or my own. He does have so much not to be modest about! Since Albert Einstein, no scientist's name has received so much media attention; unlike Einstein he has laid himself bare, displaying, if not exaggerating, every flaw in his true confessions,[5] in the genre of, and by now more widely read than, Rousseau or Augustine. Whether he has reached the age of repentance we have still to see.

Let us turn from the man to the discovery and ask:

- first, what did the double helix do for us scientifically? and
- second, how would it have mattered if that hadn't happened in 1953? (beyond that Matt Meselson would have had another year or two to finish his rotifer paper).

For my first question, let me quickly separate duplicity from helicity. The duplex and its tacit lemma, complementarity, have dominated DNA research for the last 40 years, informing every branch of biology and medicine, and I see neither the need nor have the capability to repeat this information here.[6] The duplex is at the root of DNA as an informative molecule, and of every experiment involving sequence specificity, enzymatic reactivity, biological specificity and so forth: in a word it is inseparably connected with any laboratory or vital test of its primary structure: *pace* the protein interactions, it takes one nucleotide sequence to recognize another: via duplex formation.

Helicity has been more difficult to study, and has taken second place–it is, after all, secondary structure.[7,8] But as Alex Rich began to remark, it is very much involved in the dynamics of DNA in the cell, and obviously in such spheres as regulated gene expression, transcription, and the packaging of DNA into chromatin and chromosomes. It is becoming increasingly important in the study of recombination, mutagenesis, and cancer.

With regard to my second question, it is on a different track from Gunther's–not *who* else would have discovered the structure, but *whether* it would have been discovered. What if X-ray diffraction just didn't exist as a workable method of structural analysis? We could note that only a tiny fraction of contemporary research–an important one!–actually uses those tools, nor depends on the precise molecular coordinates of DNA. Of course, that's an unfair test: who would have thought of the simpler experiments without the structural precedent?

Rollin Hotchkiss has commented on the growing consensus about the centrality of DNA in the late 1940s. Modelled on the study of protein secondary structure, and its denaturation, were the beginnings of hyperchromicity assays and their bearing on DNA secondary structure. Levene's tetranucleotides, never more than a casual heuristic, had been refuted. But the chief obstacle in my view was, in contrast to proteins, a lack of a conveniently available, homogeneous biological specimen on which to conduct biochemical and biophysical analysis. It would eventually come in the form of small bacteriophages. The virtue of X-ray analysis of DNA fibers was its insensitivity to heterogeneity of primary structure: it leapfrogged to the next level of generalization and that surely saved us ten years or more of false starts and stumbling in the dark. Nor can anyone who has actually tried to build models from scratch belittle the ingenuity and insight that went into the construction Watson and Crick made.

I also join Gunther in celebrating the 1953 papers for having generated one of the most far-reaching icons of the twentieth century–the image has even reached perfume bottles; it is redolent of–I was going to say the Caduceus, but that's single-stranded–Hermes' staff. As iconography, it is a creative artistic production that has captured the visual imagination at a symbolic level as well as an intellectual one, for the public as well as the scientific community.

For flash of scientific insight, beacon, and icon, we are all in your debt; and you deserve a little something for having endured us. On behalf of the New York Academy of Sciences, I am privileged to offer this certificate of appreciation to you, Jim Watson.

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